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A Long-term Study of a Case of Schistosoma Mansoni Subjected to Repeated Courses of Treatment

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Introduction.

The studies of the effects of treatment on individual patients suffering from bilharziasis has been a feature of the work of this Laboratory for some years. (Blair *et al.* 1969b). From this work has emerged some interesting information on the disappearance and re-appearance of eggs and miracidia when treatment has failed. The earlier work was based on specimens of urine and stool passed by the patients from Monday to Friday only.

The subject, Lovemore Manyoso, came to hand in March, 1971. He was an African male aged about 18 years and weighing 53 kg. The specimens of urine were collected and prepared as described in Blair *et al.* (1969b), and the stools as described in Blair *et al.* (1969a).

Miracidia hatching examinations were carried out at 1000, 1200 and 1500 hours, using the techniques described by Weber (1973).

Method.

Stool and urine specimens were obtained from this patient for a few days prior to the first treatment to be sure he understood how to pass his mid-day terminal urine and take a sample of stool. No attempt was made to show him what part of the stool should be taken for examination, especially as at this stage his stool was not formed.

Specimens taken by the patient on Saturday, Sunday and Monday were processed on Monday. Miracidial hatching examinations were carried out at 1000, 1200 and 1500 hours, which meant that each tube was examined at least eight times — twice the day of processing the stool, and three times on each of the following two days. When the week-end broke the routine, one examination was done on Saturday morning and carried on three times on Monday.

The Trial.

It was established that the patient had a double schistosome infection; *S. haematobium* in the urine and *S. mansoni* in the stool. The urinary infection was very light, showing only 10 to 20 eggs in a mid-day terminal urine sample. Miracidia were freely hatched. This infection disappeared completely after the first course of treatment.

In the case of his stool infection, the egg counts on the samples of early morning stool ranged from 260 to 430 *S. mansoni* eggs, and miracidia were seen at each examination of the specimens over a three-day period, ranging from + to 4+, the latter being the second highest categorv in estimation of miracidia seen.

The grading of active miracidia seen cannot be done with accuracy for such fast-moving larval forms, but does give a reliable index of the numbers present when estimated by experienced observers.

Physically the patient was a stockily-built youth and had no other signs or symptoms except that the liver was easily palpable under the right costal margin, and was tender in this area on deep palpation.

Treatment.

The following attempts at therapy were made:—

1. On 27th March, 1971, with the patient's weight at 53 kg he was given an intramuscular injection of 160 mg hycanthon (Etrenol Winthrop), a dose of 3,0 mg/kg. The egg counts in urine and stool on the day of treatment were 10 and 4309 respectively, and miracidia hatched in each case in the stool up to a 4+ rating. He showed no toxic or any other side-effects to treatment.
2. From 17th to 22nd May, 1917, he was given niridazole (Ambilhar CIBA), 750 mg each morning and 1 000 mg in the evening for six days. As his weight was now 54 kg this represents a daily dose of 32,4 mg/kg. He carried on his work as a gardener without interruption, but admitted he had slight nausea on the afternoon of the third day of treatment.
3. On 17th August, 1971, he began a second course of niridazole. His weight was now 55 kg and he was given 750 mg morning and evening for six days; 27,3 mg/kg. One hour after the first dose of niridazole was taken he was given an intravenous injection of 65 mg sodium antimony tartrate (S.A.T.) This was given in the hope

that the antimony might free the hold of schistosome worms in the smaller tributaries of the portal vein and allow themselves to be swept up to the liver where they might be subjected to higher concentrations of niridazole. The only side-effect experienced was some joint pain, including pain in the temporo-mandibular joints, a site where pain had been reported previously after niridazole therapy. Prior to this treatment the liver was easily palpable below the costal margin and there was slight tenderness on palpation in the mid-line.

4. On 26th October, 1971, his weight was 56 kg and he was given 180 mg of hycanthone intramuscularly; 3,2 mg/kg. An hour later he was given 100 mg S.A.T. intravenously with the same objective as described above.
5. On 4th April, 1972, his weight had fallen to 54,5 kg, his liver was easily palpable and slightly tender in the mid-line. He was given an intramuscular injection of hycanthone; total dose 170 mg; i.e., 3,1 mg/kg.

Follow-Up Analysis.

Table I summarises the egg counts and hatching estimations before and after each treatment.

It will be seen that hatching miracidia generally continued to be observed after microscopic evidence of eggs had disappeared, and that miracidia re-appeared generally before the presence of eggs was detectable on microscopic examination.

From March, 1971, to May, 1972, a morning stool sample was taken by the patient on 398 days, and the following is the summary of the findings. They were:

231 days on which eggs were seen and miracidia hatched;

9 days on which eggs were seen, but no miracidia were hatched;

105 days on which no eggs were seen, but miracidia were hatched; and

55 days when there were no eggs seen and no miracidia were hatched.

Despite five separate treatments during this period the patient continued to pass eggs or miracidia were hatched on all the days observed except for 55 days; this is rather surprising.

The results demonstrate very well the value of miracidia hatching as a sensitive and reliable method of diagnosis in *S. mansoni* bilharziasis, especially in the follow-up programme after treatment when eggs are sparse in the stool specimen. Over this period, relying only on microscopic examination for eggs, evidence would have been found on 240 days while by miracidial hatching alone this would have been seen on 335 days. Using only microscopic methods of examination, only 70 per cent. of the days when evidence of stool infection existed would be detected, while using miracidial hatching, 97 per cent. would be detected.

Table I.

Daily S. mansoni Eggs and Miracidial Hatching in Relation to Repeated Treatment.

No. and date of treatment		Drug Used	Pre-treatment		No. of days to disappearance of		No. of days of absence of		No. of days from end of treatments to return to steady output of eggs and miracidia
			Eggs	Hatch	Eggs	Hatch	Eggs	Hatch	
1	17-3-71	Hycanthone	430	4+	16	21	14	9	44
2	17-5-71 to 23-5-71	Niridazole	130	3+	21	21	5	5	49
3	17-8-71 to 23-8-71	Niridazole + S.A.T.	30	+	5	11	10	3	17
4	26-11-71	Hycanthone + S.A.T.	90	3+	8	18	24	3	63
5	4-4-72	Hycanthone	60	+	17	17	15	15	59

S. mansoni egg output:

Prior to treatment, the patient's weekly egg count was established to be over 2 000 per week. The three re-treatments, given in May, August and October, 1971, were given as soon as it was obvious from the egg count levels and the miracidial hatching that the previous treatment had not destroyed all *S. mansoni* worms. After the fourth treatment given on 26th October, 1971, had also failed to achieve this objective, it was decided to continue the daily follow-up examinations for a longer period in order to see whether there was any trend in the daily egg production and miracidia hatching.

When only a small number of eggs were to be counted in the week's specimens, and miracidial hatching was scanty, it is probably better to study the result of summing the eggs counted in the seven daily specimens examined in a week. Miracidial output intensity and duration was assessed by summing for one week's samples the number of times the samples were examined over a three-day period, generally eight times for each. The procedure is best illustrated by an example of miracidial hatching. On a specimen of 7th July, 1972, the first day at 12 noon and 1500 hours, and on the second and third dav at 1 000, 1200 and 1500 hours, the miracidia hatch ratings were +, 2+, +, +,+, 2 —, +, —; a total of eight in eight examinations. The summing of the miracidial hatchings for this week was, in fact, 48 in 56 observations. From the week commencing 7th May, 1971, no eggs were seen for three weeks, 10 in the fourth week, and the miracidia hatch was very scanty and were seen in only 6/59, 3/56, 15/57 and 15/58. For the week commencing 5th December, 1971, eggs seen totalled 70, and miracidia seen on 13 occasions in 57 observations. Four weeks later, the week commencing 2nd January, 1972, egg output was 150 and miracidia seen 43/58. A further five weeks later, during the week beginning 6th February, egg output was 630 and miracidia 47/58. Thereafter the weekly egg output ranged from 300 to 500 and on a number of occasions each week 2+ miracidia hatchings were recorded. The situation was that after over a year's observation and four treatments with schistosomacidal drugs, the egg output was reduced to about 10 per cent. of the pre-treatment level, but there was no doubt about the viability of the surviving worms and their eggs. The fifth course of treatment was given on 4th April, 1972.

Twelve weeks later, the week beginning 2nd July, 1972, 110 eggs and miracidia seen on 48/56 observations and 2+ hatches were registered on three occasions. The weekly egg output was now down to about five per cent. of the pre-treatment level, but there was still no doubt of the viability of the infection. It was decided at this stage to desist from any further attempts to treat him with hycanthone and niridazole.

Discussion.

The conditions of Lovemore Manyoso's ensuch that re-infection during this time can be ruled out. Nevertheless he, in company with vironment during the course of this study were his cousins, the Mavida brothers, whose accounts appear in earlier papers of this supplement (Blair & Weber, 1973) and in the previous issues of this *Journal*, show the same pattern of marked reduction in *S.mansoni* egg output and imracidia output after their first course of treatment, but a continuance of evidence of infection at a lower level. The persisting infection showed a disappointing response to repeated treatment.

The disappearance of eggs and miracadia after treatment, the freedom from eggs and miracidia, and the eventual return of eggs and miracidia, show the value of miracidial hatching as a means of observing infections after treatment. There appears to be no significant difference in the disappearance, absence and reappearance of eggs and miracidia after each treatment, except in the case of the second niridazole treatment on 17th August, 1971. In this treatment, although eggs and miracidia disappeared from the daily stool specimens soon after the end of treatment, the days from the end of treatment to a return of steady output of eggs and miracidia was only 17 days, which is less than one-third of the time taken to get back to this level after the other four treatments. Neither drug — three treatments of hycanthone and two with niridazole — caused any inconvenience to the patient, or any real toxic side-effects. Field trials in Rhodesia have shown that either drug will "cure" about 75 per cent. of patients and the other 25 per cent. will show "improvement" with great reduction in the number of eggs passed, and improvements in their health and physical condition. Further and repeated treatment with one or other of the two drugs mentioned produces very little reduction in egg output. Improved and more sensitive methods of the diagnosis of *S. mansoni* bilharziasis show that many patients whose follow-up examinations include routine and proper miracidia hatching, will be found not to be cured; many of these patients would have been assessed as "cured" if the examination consisted of only a single microscopic examination of stool, perhaps only on a simple direct smear.

The fate of the 25 per cent. of *S. mansoni* patients who are not cured by a single course

of treatment with one of the modern agents has been a matter of great interest and concern over the past four years. The disappointing results of repeated treatments has raised a number of controversial points as to what action, if any, should be taken.

There is no doubt that one treatment will "cure" or "improve" the great majority of patients. Re-treatment of those who are not "cured" shows disappointing results, and up to 10 courses of treatment have been given without eliminating all stool egg production.

1. *Are some strains of S. mansoni resistant to the newer drugs?*

It is interesting to note that three young Africans suffering from *S. mansoni* infections, who come from the same locality, were not cured easily. On the other hand, similar poor results on repeated treatment have been observed and reported from other areas in Rhodesia unconnected with the Zambesi Valley area. Failure to cure has not been an exclusive feature of young patients, but is also seen quite frequently in adults — even older adults. At one stage it was thought that the livers of younger patients are less damaged than those of their elders, and so metabolise the drugs speedily before they could exercise their full effect on the worms.

2. *Where in the portal system do the modern drugs act on the worms?*

In the days up to and immediately after World War II when antimonials reigned supreme in the treatment of bilharziasis, much attention was directed to the study of the "liver shift" of worms, which was said to occur when antimony was administered. Cautions were stated that any schedule of treatment which caused a massive shift of worms to the liver could be dangerous causing severe and even fatal liver damage. The suggestion was that the worms had to be encouraged to shift from their egg-laying sites to the liver to be subjected to the lethal effects of anitomy. With the newer drugs, niridazole and hycanthone, one hears fewer comments on the danger of "liver shift" of worms and damage to the liver. Do these drugs circulate from the liver to the arteries serving the organs where worms are sited and causing them to be swept up to the liver where the drug would eventually destroy the worms? Perhaps the modern drugs are much less effective than antimony in releasing the hold of the worms in the mucosa of bowel, although they seem, from experience of cure, to be so effective in destroying *S. haematobium* worms This might explain why *S. mansoni* worms remaining in their egg-laying sites cease egg production after treatment, only to start again when the drug is no longer present. Perhaps further treatment of the same nature has just as little effect on the lives of the worms as the first treatment.

3. *Should one be satisfied with "cure" of say, 75 per cent. of patients and reduction of worm load in the remainder after a single course of treatment?*

From the public health viewpoint such a result is of great value in the reduction of infection of surface waterbodies. The younger age groups of the population show the highest prevalence of bilharziasis; they generally have greater individual worm burdens; their habits and actions often result in fouling of surface waterbodies and so a big reduction in the output of hatchable eggs is bound to reduce the infection potential of the water environment. The improvement in general health, weight gain, improvement in skin tone and conditions, and in mental and physical achievement, is difficult to measure, but undoubtedly occurs, although so far few studies have produced valid scientific evidence to this effect.

The presence of a few residual worms in the bowel wall laying a small number of eggs may actually be an advantage to the host. If only minimal damage is done at the egg-laying sites, this may help the host to maintain and develop a resistance to future challenge infections.

SUMMARY.

A patient with an *S. mansoni* infection was treated and re-treated on a total of five occasions with hycanthone or niridazole over a period of 15 months, and still continues to pass hatchable *S. mansoni* eggs in the stool at a level of about five percent. of that existing prior to treatment. Certain suggestions and thoughts are put forward concerning re-treatment and how far this should go.

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